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GOLD

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From wedding rings on fingers to massive ingots in government vaults, by way of Olympic medals and stained glass windows, gold has been highly prized for millennia. Its contribution to metaphor alone is legion — who would want a therapy that is, let us say, the silver standard?

Element 79 in the periodic table has a celebrated place in the history of science and technology. Ernest Rutherford figured out the basic architecture of the atom — a tiny nucleus orbited by distant electrons — by shooting alpha-particles at gold foil and seeing that most went straight through it. Michael Faraday's experiments with colloidal gold gave an early hint of today's nanotechnology revolution. And gold electrodes were used in the earliest integrated circuits — the chips that launched the information revolution.

The rising price of gold has driven mining companies to places previously deemed too difficult or expensive, and recycling plants extract large amounts of gold from discarded mobile phones, computers and other electronic jetsam (see page S4). Microorganisms can help too — bacteria have been found that make gold nanoparticles from solutions of gold salts (S12).

Nanoparticles are at the heart of gold's most exciting technological developments. Gold nanoparticles can carry drugs directly to tumours without damaging healthy tissue (S14), for example. The striking visual qualities of gold hint at remarkable properties found only at extremely small dimensions. The so-called plasmonic effect, which gives stained glass windows their iridescent beauty, is especially pronounced when using gold (S7); this property could lead to better electronic and photonic devices, such as more efficient solar cells (S8). And chemists are discovering that although gold is usually chemically inert, it can be an extremely effective catalyst (S10).

We acknowledge the financial support of the World Gold Council in producing this Outlook. As always, *Nature* has full responsibility for all editorial content.

Herb Brody
Supplements Editor

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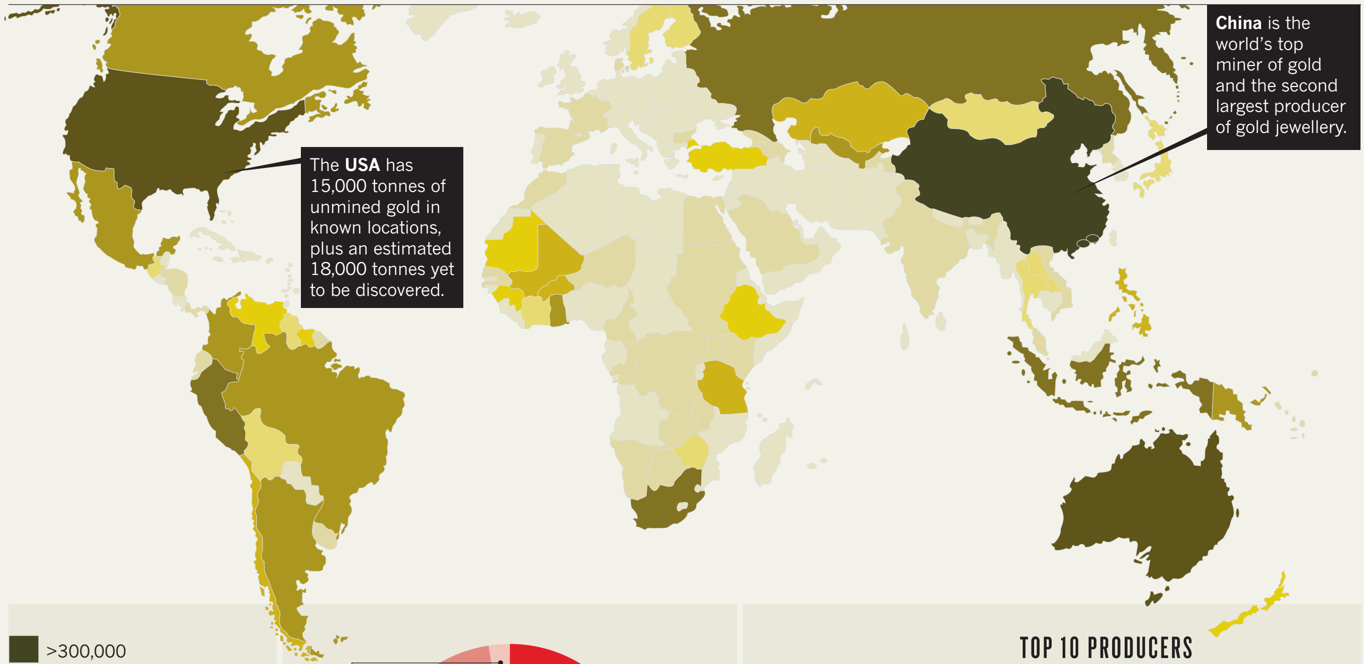
MINE, ALL MINE!

Throughout history, gold has been prized around the world and eagerly sought. But where does it come from, and where does it all go? By **Neil Savage.**

$89T
Total value of all mined gold in trillions of US Dollars

WHERE DOES GOLD COME FROM?

World gold production 2010



- >300,000
- 200,000–300,000
- 100,000–200,000
- 50,000–100,000
- 25,000–50,000
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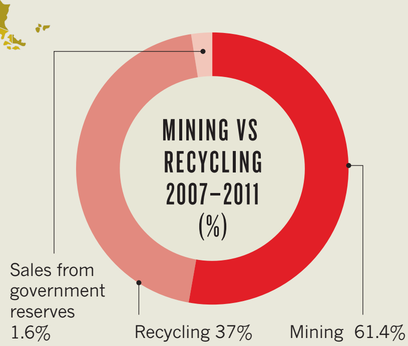
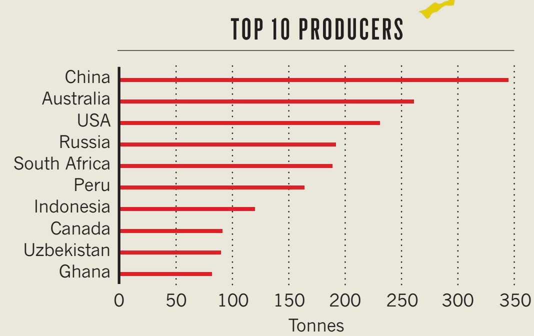
- 5,000–10,000
- 1,000–5,000
- <1,000

Tonnes





GOLDEN MILESTONES

Key moments in the use of the precious metal in science and technology

ca. 700
The Etruscans use gold bands in dentures.

1803
Luigi Brugnatelli of Italy electroplates two silver medals with gold.

1848
California's Gold Rush starts the extraction of more than 90% of the gold ever mined.

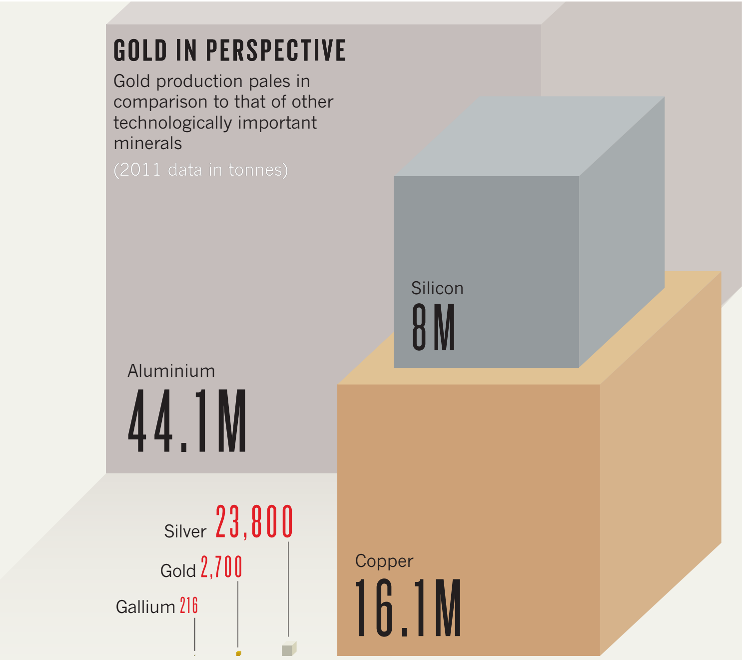
1856
Michael Faraday experiments with suspensions of gold in solution.

1887
Invention of the McArthur–Forrest process using cyanide to extract gold from low-grade ore.

GOLD IN PERSPECTIVE

Gold production pales in comparison to that of other technologically important minerals

(2011 data in tonnes)



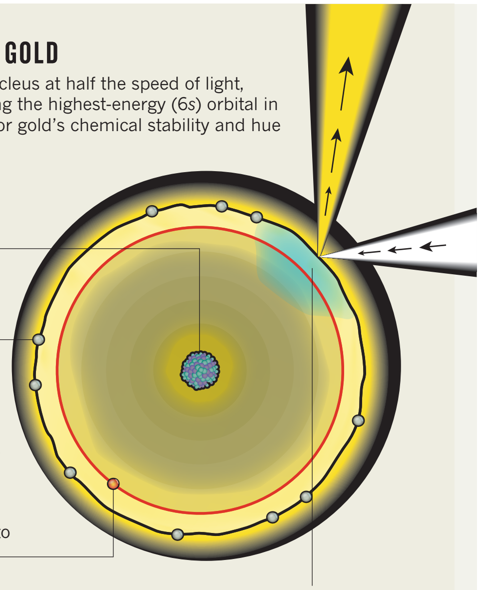
THE PHYSICS OF GOLD

Electrons orbit the nucleus at half the speed of light, relativistically shrinking the highest-energy (6*s*) orbital in a way that accounts for gold's chemical stability and hue

Nucleus contains 79 protons and 118 neutrons

5*d* orbital is relativistically enlarged

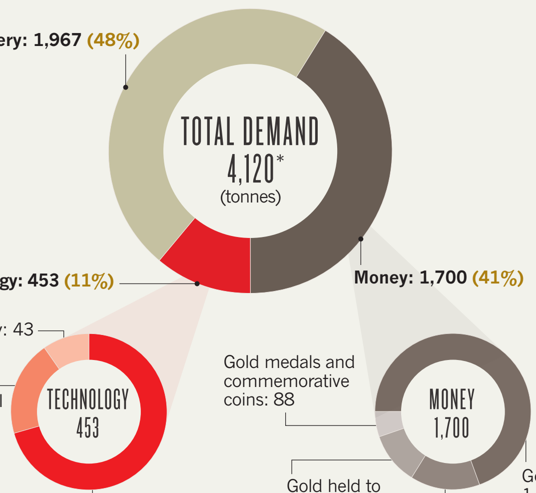
6*s* orbital is relativistically shrunk so this high-energy electron is, on average, closer to the nucleus than are the 5*d* electrons, making it less available to bind to other atoms



Relativistic effects shrink the energy gap between 5*d* and 6*s* electrons so the atom absorbs blue light; what we see is a combination of the other colours in the spectrum, which add up to a golden hue

WORLDWIDE DEMAND FOR GOLD IN 2011

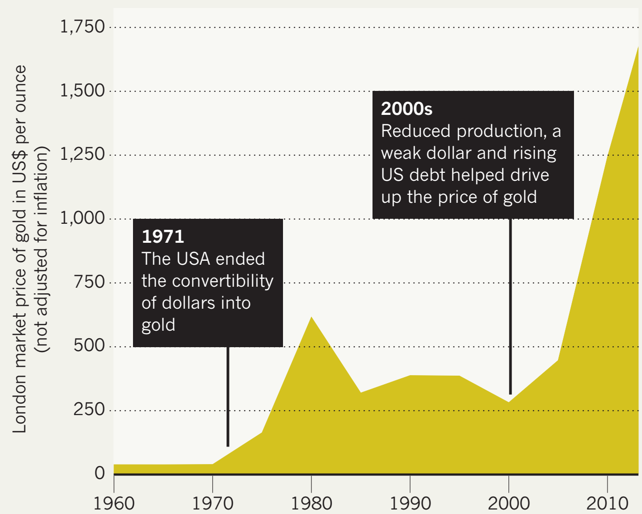
Gold is mostly required for jewellery, technology and money



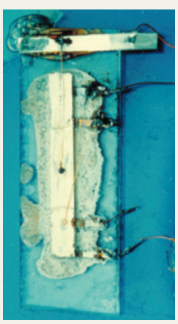
*Not including purchases by central banks

PRECIOUS COMMODITY

The price of gold, long set by governments, remained steady from the early eighteenth century well into the twentieth century

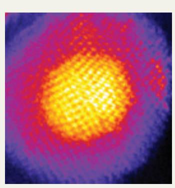


1911 Ernest Rutherford shoots alpha-particles through gold foil to reveal the existence of the atomic nucleus.



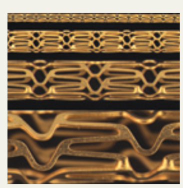
1957 Jack Kilby uses gold wire connectors in the first integrated circuits.

1985–1987 Masatake Haruta and Graham Hutchings demonstrate the use of gold as a catalyst.

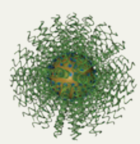


1996 Chad Mirkin and Paul Alivisatos use DNA to build gold nanoparticles.

2000 Boston Scientific starts selling a gold-plated stent for heart surgery.



2012 The FDA approves Verigene, a gold nanoparticle diagnostic device to identify infectious bacteria.



MAP & TOP 10 PRODUCERS: US GEOLOGICAL SURVEY/$89T NUMBER, & MINING VS. RECYCLING: THOMSON REUTERS GFMS/GOLD IN PERSPECTIVE: USGS MINERAL COMMODITIES SUMMARY 2012/WORLDWIDE DEMAND FOR GOLD: WORLD GOLD COUNCIL/PRECIOUS COMMODITY: NATIONAL MINING ASSOCIATION.

TOM FOX/DALLAS MORNING NEWS/CORBIS

Miners walk between elevators en route to the depths of South Africa's TauTona mine, the world's deepest gold mine, 4 km below the surface.

MINING

Extreme prospects

High gold prices are making it worthwhile to look for gold in some unusual places.

BY BRIAN OWENS

The journey from the surface to the rock face at the bottom of TauTona, the world's deepest gold mine, takes almost an hour — even with the lifts that bring the workers down each of the mine's three shafts travelling at 58 km per hour. In the dark, hot, cramped tunnels nearly 4 km underground, workers excavate a thin dipping vein of gold ore. Rock is taken to the surface and the gold is extracted using a process that can be traced back to the 1880s: the ore is crushed and sprayed with cyanide to leach out the gold metal.

Gold has always been a valuable commodity, but over the past 10 years the price has risen dramatically — from less than US$400 per ounce in 2003 to almost $1,700 at the end of 2012. At the same time, gold production has seen only marginal increases, with few new mines opening. And it's getting a lot more expensive to extract the gold. In 2000, the average cost of extracting an ounce of gold was just over $200, says Jason Goulden, director of metals and mining at the SNL Metals Economics Group in Halifax, Canada. By 2010, he says, it had risen to more than $850.

Demand has never been higher, but nearly all the easy gold has already been mined. So, to maintain production, mining companies are turning to more difficult sources that would have been left in the ground if gold prices had been lower. From the depths of TauTona in the South African veldt, all the way up to Pierina in the Peruvian Andes, 4,100 metres above sea level, miners are digging deeper than ever before, going to more remote locations and politically volatile regions.

At the same time, significant amounts of gold can easily be obtained without digging into the earth at all — just by recycling the gold buried in the growing mountains of discarded electronics. The advent of more efficient ways to recycle gold from gadgets has turned scrap into a major source of the precious metal.

DIGGING DEEP

There are many factors that influence where and how deep a mining company will dig for gold, but in general "as you go deeper it gets

THINKSTOCK

more expensive and time-consuming", says Steve McKinnon, a mining engineer at Queen's University in Kingston, Ontario, Canada, who specializes in designing deep mines. It also gets more dangerous.

Mining at depths such as those of TauTona presents many unique challenges in protecting the miners, says McKinnon. First of all, it's hot. The temperature at TauTona's deepest levels is a stifling 58 °C. Air conditioning brings the temperature down to a toasty but more tolerable 28 °C.

Then there is the risk that digging can fracture the rock around the pit, triggering a seismic event. "Sometimes that fracture process can be very violent, because the rock behaves in a brittle manner," says McKinnon. "There have been events larger than magnitude 5" — equivalent to a moderate earthquake.

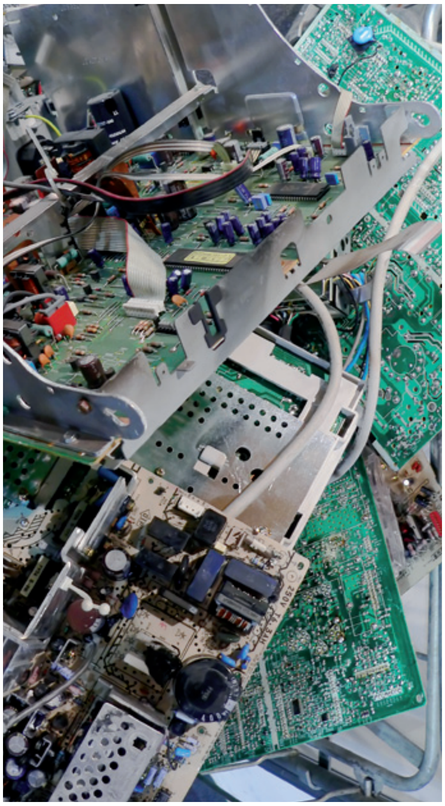
To minimize the risk, mines use 'yielding supports' that are able to deform as the tunnel walls move yet still retain their ability to support the structure. There are also networks of seismic sensors that constantly monitor the rock and develop a seismic 'fingerprint' for the region — any departure from an established baseline requires that workers be pulled out until seismic readings return to normal.

Engineers specializing in rock mechanics, such as McKinnon, also try to design mines in such a way as to minimize and control the forces exerted on the rock. Taking into account data on local stresses on the rock, and other factors such as the presence of nearby faults, they calculate the most favourable layout and method of ore extraction to minimize fracturing. This information helps engineers determine which bits of rock can be safely removed and which need to be left behind to support the rest — in much the same way as an architect decides where to put the pillars in a cathedral to hold up the enormous roof. This design modelling is "really at the limit of our technical ability now", says McKinnon.

But other new technologies are also making deep mining safer and easier. Self-driving trucks, for example, don't mind working in the baking heat. And while a robot buried in a rockfall would be an expensive loss, it's not a tragedy.

"We've got robotic vehicles that can drive, but there's still a lot of missing pieces when it comes to integrating them with the mining process," says Joshua Marshall, a robotics engineer at Queen's who is developing robotic vehicles. Marshall says these robots will eventually be efficient, safe and save money. The 'load–haul–dump' machines that transport ore and waste from the rock face to the surface are already pretty good at hauling and dumping autonomously, but they still need human help to load up. Marshall's group is developing a loading algorithm to fix that.

Marshall is also dealing with a major stumbling block to fully automated underground mining: knowing where all your robots are at any given time so they can be coordinated to move and work in the most efficient way. Open-pit mines already use global positioning system (GPS) to move their automated vehicles around in a way that maximizes productivity, but such satellite signals can't penetrate deep underground. Radio signals can't be used either because they bounce around too much inside the tunnels.



E-scrap has 250–350 grams of gold per tonne, far more than the 1–5 grams of a typical mine.

So Marshall's group is trying something different, using laser scanners to construct detailed three-dimensional maps of all the tunnels and mounting similar scanners on the vehicles. A robot can then find its location by comparing the map with the features its scanner can 'see' on the tunnel walls. "We don't rely on radio signals or trying to penetrate anything through rock, we just use the features of the environment themselves," he says. Several mining companies, keen to apply the efficiencies available through GPS above ground, have already shown an interest, Marshall says.

WASTE NOT

The high gold price and new technologies are also allowing companies to make use of easily accessible ores that were once considered to be too much trouble, such as those containing a mixture of copper and gold. These copper–gold ores are "a pain in the neck" to deal with, says John Monhemius, a mineral engineer at Imperial College London, because the cyanide used to leach gold from the ore tends to grab too much copper. In the worst cases the process doesn't pick up any gold at all — or so little that it's almost impossible to separate it in solution. Moreover, the activated carbon that is used to absorb the gold from the cyanide solution is also swamped by the less valuable metal.

New ion-exchange resins, developed by Johannesburg-based mineral research organization Mintek, are far more selective. These resins can extract the gold from solutions that contain 1,000 times more copper than gold, as found in the leach solution from the Gedabek gold–copper project in Azerbaijan. Although the resins are around five times more expensive than the conventional carbon used, Monhemius believes that high gold prices will result in this resin technology eventually displacing carbon in nearly all forms of gold extraction.

REUSE AND RECYCLE

Some companies have turned to a more reliable source: reclaiming and recycling gold that has already been mined. This 'urban mine' of electronic waste — old computers, mobile phones and the like — is far richer than natural deposits: a typical open-pit mine will yield between 1 and 5 grams of gold per tonne, but mobile-phone handsets can contain up to 350 grams per tonne of gold, and computer circuit boards up to 250 grams.

The explosion in the use of electronics over the past three decades has, in effect, created another kind of gold mine. Indeed, with legislation setting targets for the collection and treatment of electronics, recycling the precious metals from such waste has become a lucrative business, says Christian Hagelüken, a mining engineer who specializes in recycling materials from scrap electronics at Brussels-based Umicore, a leading precious-metals recycling company.

The process for extracting the gold and other precious metals from a pile of circuit-boards and mobile phones is straightforward. The material is shredded and sent to a huge smelting furnace, where it is melted down at 1,250 °C. Two phases form, a metallic layer of mainly copper on the bottom, and a slag layer on top. The precious metals, having a high affinity for copper, are dissolved in the bottom layer. Once cooled, the bottom layer is ground into a fine powder and mixed with sulphuric acid to dissolve the copper and leave behind the precious metals (the copper itself is also purified and sold). Then the various metals — gold, silver, platinum and others — are separated in a series of steps involving precipitation, distillation and ion exchange.

The innovation has come in the development of sophisticated recycling facilities such as Umicore's plant in Hoboken, the Netherlands. Such plants are entirely closed-loop systems, with companies finding a use for every bit of waste. Lead and other base metals can be refined from the slag, and even the sulphuric acid used to leach the precious

DIRTY GOLD

The seamier side of mining

Gold mining can be a dirty business, both environmentally and ethically. Extracting gold from the mined ore creates a huge amount of waste — roughly 20 tonnes of mining waste to make a single 18-carat ring containing less than 10 grams of gold, according to an estimate from Earthworks, an environmental watchdog based in Washington, DC. What's more, many small-scale operations in the developing world make use of child labour, and can support civil wars or local warlords.

The US Environmental Protection Agency rates the metal mining industry as the number one toxic polluter in the country in its Toxics Release Inventory 2011. A large part of this pollution is cyanide, the main chemical used to leach gold from crushed ore; it can contaminate surface and ground water if it leaks from waste sites. One of the worst such accidents occurred in Romania in 2000, when a burst dam sent cyanide-contaminated water into the Someş river, and eventually into the Danube. It killed large numbers of fish and poisoned the drinking water of more than 2.5 million people.

Mining companies often say that new technologies will make mining cleaner, says Alan Septoff, communications director at Earthworks, but that is rarely the case. Research commissioned by Earthworks found that, in the United States, "75% of mines wind up polluting water, no matter what they promise," he says.

This is at least partly because nothing is quite as effective as cyanide at getting gold out of rock. There have been attempts to find less dangerous chemicals, but they have been largely unsuccessful, says John Monhemius, a mineral engineer at Imperial College London. Thiosulphate, thiocyanate, perchlorate, chloride and bromine have all been tried, but none can match cyanide's specificity for gold.

"I did quite a lot of work on thiocyanate, but in the end I decided it wasn't any better than cyanide," Monhemius says. Although it is not as directly poisonous as cyanide, thiocyanate requires much higher concentrations so the results of an accidental spill would be just as bad — possibly even worse, he says. "Cyanide suffers from a lot of bad press," Monhemius adds. "If it is used properly, it doesn't cause a threat to the environment."

The gold mining industry's voluntary International Cyanide Management Code provides guidelines to ensure the chemical is manufactured, transported and used safely.

REUTERS/CORBIS

In 2000, a burst dam sent cyanide from a Romanian gold-processing plant into local rivers, killing large numbers of fish.

Unwanted neighbour

Gold mines can be a source of great wealth but they are not always welcomed by the local population. In Peru, for example, massive protests and nationwide strikes against the planned Conga gold mine eventually led to the suspension — although not the cancellation — of the project in 2012. People were concerned that the amount of water the mine would use would endanger agricultural and drinking water supplies in the region.

Earthworks is running a campaign called No Dirty Gold, which aims to encourage consumers to pressure the mining industry to be more environmentally and socially responsible. The industry is engaging with Earthworks and other civil society groups, says Septoff, although the two sides have not yet agreed on what "responsible mining" should look like.

In October 2012, the mining industry issued a Conflict-free Gold Standard that companies can use to certify that none of the proceeds of their gold — including any bought from local small-scale operations — is supporting "unlawful armed conflict". The first public announcements by companies that they are complying with it, which must be externally verified, are expected in early 2014 when they report on their 2013 activities.

Gold not green

But even avoiding mining by recycling gold from scrap electronics is not always the ethical or environmentally friendly option. Although advanced plants, such as precious-metal recycling firm Umicore's closed-loop facility in Hoboken, the Netherlands, release very little waste, this standard is not universally followed. In fact, much electronic waste is sent to the developing world, where piles of televisions and computers are burnt under the open sky, with cyanide poured over the slag to extract the precious metals. This not only releases dangerous fumes and chemicals, but also results in low yields.

"It is obvious that from an environmental and social point of view this unregulated recycling is a disaster," says Umicore recycling engineer Christian Hagelüken. The electronics recycling industry must be better managed and regulated, he says, to stop dangerous and wasteful operations. — ***B.O.***

metals from the copper is a by-product of one of the gases produced by the furnace. As well as being environmentally friendly, modern plants like these have yields "close to 100%", says Hagelüken.

The challenge lies in ensuring that the electronic devices reach such sophisticated plants at the end of their life — only a fraction of e-scrap currently does. The United Nations Environment Programme estimates that just 15% of the gold in waste electronics is recovered properly. Huge amounts are left sitting in drawers and attics, or worse, sent to landfill or incineration plants. "The one important point is how to boost collection," says Hagelüken, and ensure it is recycled properly.

But even with much higher recycling rates, e-scrap will never be able to supply our insatiable demand for gold. So the value of gold will continue to drive the miners of TauTona to ever greater depths. ■

Brian Owens *is a freelance science writer based in St Stephen, New Brunswick, Canada.*

PERSPECTIVE

A glint of the future

The same property that gives stained glass windows their sublime beauty is being crafted in the latest nanophotonic technologies, says **Anatoly V. Zayats**.

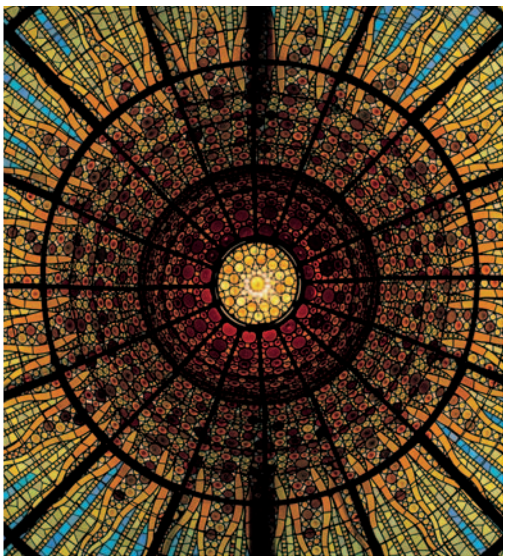
We live in what could be described as the era of photonics: in information technologies, data are transmitted in pulses of light; light-emitting diodes (LEDs) provide energy-efficient lighting; and optical sensors are able to detect diseases and explosives.

For many years, gold and other metals have been used in optics and photonics as a mirror coating — a function based on the metal's freely moving electrons, which also allows them to conduct electricity. Shine white light on a gold bar and you'll see a yellowish reflection. However, it is possible to tune the colour of gold nanoparticles to green, orange, red or anything in between. The phenomenon gives rise to the brightly coloured stained glass windows in medieval palaces and cathedrals, for example.

The apparent colour of gold nanoparticles is determined by oscillations of the nanoparticles' free electrons, which are excited by photons striking the metal's surface. Light forces the electrons in the metal to move together, creating a so-called plasmon — a collective of electrons vibrating in phase with each other[1]. It's the plasmons that influence the scattering and absorption of light by metal nanostructures and lead to the colourful stained glass. With plasmonic nanostructures, one can manipulate light at a much finer scale than it is possible to achieve in conventional photonic devices.

Plasmonics underlies several important nanotechnology applications, including nanoscale lasers, optical data processors, biological and chemical sensors, cancer therapy, high-density data storage, and improved photodetectors and solar cells, thanks to the metal's ability to confine light to dimensions smaller than its wavelength.

SYLVESTER ADAMS



Can gold plasmonics be as useful as it is beautiful?

Gold is not actually the best metal in terms of optical properties alone. That prize goes to silver, which absorbs less light in the visible and infrared ranges. Silver's optical response is almost the ideal response of free electrons. In gold, electron transitions between energy levels correspond to the visible wavelengths. These transitions, which give rise to gold's characteristic yellow glitter, are also responsible for the metal having a higher optical absorption than silver. This drawback may exclude the use of gold from some applications, such as 'perfect' (diffraction-limit-free) lenses that can focus light with unprecedented precision. But in other plasmonic applications, gold is turning out to be ideal.

Biosensors are a good example. Gold exhibits unmatched chemical stability in the ambient environment, and gold nanostructures preserve their properties for many years. By contrast, silver, which may initially provide better performance, loses its lustre and plasmonic properties within days. Another big advantage of gold for biosensing is that its chemical interaction with organic compounds is extremely well understood. Take, for instance, so-called 'label-free biosensing techniques', which negate the need for dyes or radioactive tracers in biochemical assays. Achieving sensing selectivity requires initial 'functionalization' of a gold surface — the attachment of sensed molecules — which then modifies the plasmonic resonance, leading to a detectable colour change. The current drive is towards miniaturization. The ability to add precise nanostructures to gold surfaces makes it possible to incorporate this technique in lab-on-a-chip systems[2].

Gold's properties also make it well suited to nanophotonics, in which plasmonic signals are used to guide and control optically transmitted information. Such manipulation involves a plasmonic device with nonlinear optical properties[3]. One approach to building such devices is to combine metal nanostructures with conventional dielectrics. But this requires more complex fabrication steps, and such dielectrics limit the switching speed that is fundamental to digital information processing. It's better to avoid the use of dielectrics altogether and rely on the high-speed nonlinear responses of a metal.

In gold, the nonlinear response determined by plasmonic lifetime is less than 10 femtoseconds — about five times faster than in silver[4]. The nonlinearity is also stronger than in silver. In fact, gold's high and fast nonlinearities may lead to optical switches that are faster than electronic ones — a development that could have enormous consequences as information processing migrates into the optical realm.

What may prevent the widespread use of gold in some plasmonic applications is incompatibility with silicon and its low melting point (1,064°C), which might be especially problematic for engery concentration, for example, in heat-assisted data storage.

As plasmonics grow in technological importance, other materials will vie for attention. They will probably be less expensive than gold, but also less versatile. With its combination of chemical and optical properties, gold is likely to take the winner's medal in the plasmonics competition for many years to come. ■

Anatoly V. Zayats *is a physicist at King's College London specializing in nanophotonics and plasmonics.*
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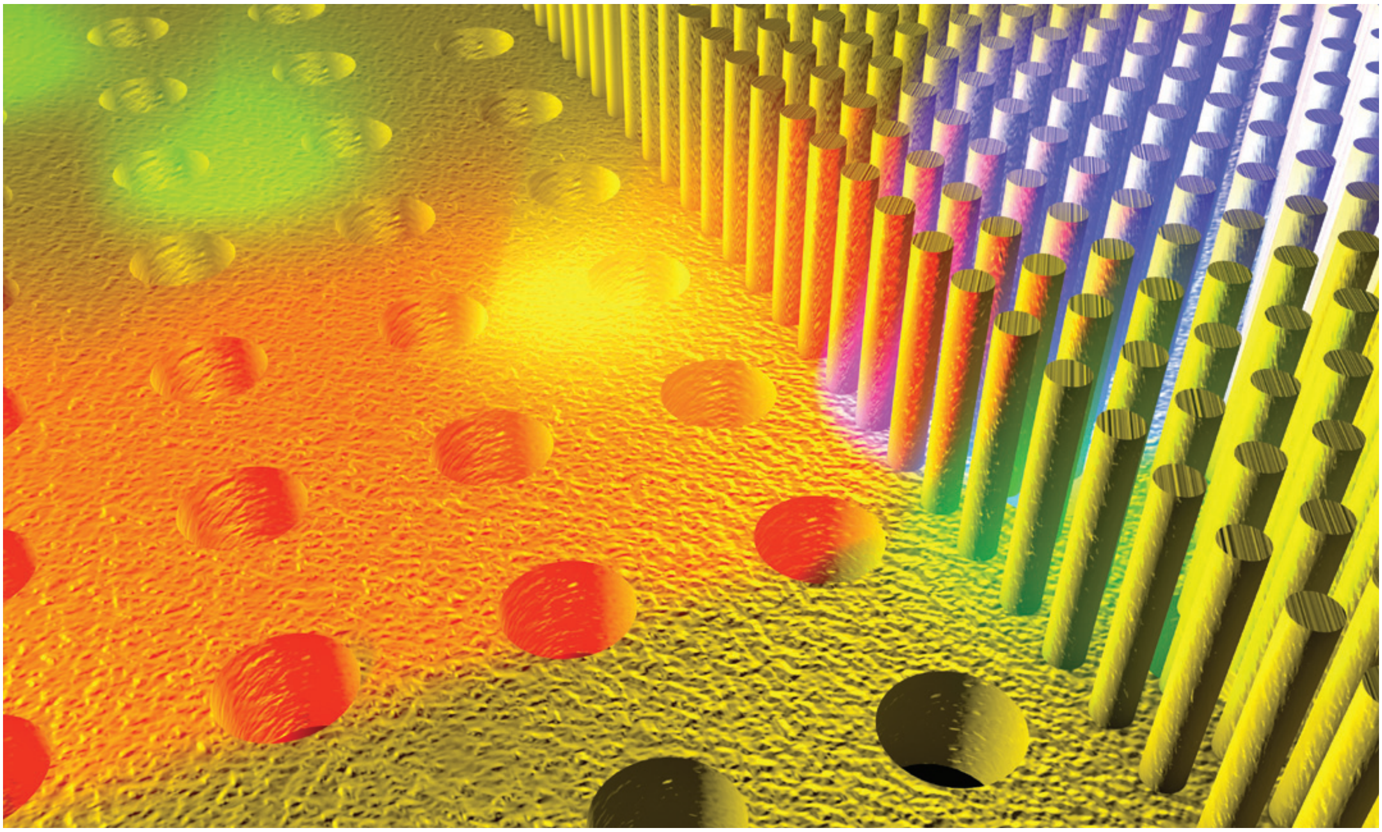

RYAN MCCARRON, KING'S COLLEGE LONDON

Because of their interaction with light, called plasmonic resonance, gold nanoparticles can be used to make effective sensors and efficient solar cells.

PHOTONICS

Trick of the light

Invisibly small particles of gold can be used to manipulate the properties of light.

BY NEIL SAVAGE

A very special piece of glass can be found at the British Museum in London. Forged into a chalice in the fourth century, it depicts the mythological King Lycurgus being trapped by a vine after he attacked the god Dionysus. What sets this cup apart from other ancient artefacts is the way it interacts with light — in ambient light it is jade in colour, but when light shines through it, it glows bright red.

This striking phenomenon arises from tiny beads of gold and silver, about 70 nanometres in diameter, embedded in the glass. At these dimensions, a phenomenon called surface plasmon resonance takes effect: light striking the metal's surface resonates with the metal's electrons, redirecting colours of light in unusual ways.

Gold has a long history in electronics and optics, from corrosion-resistant electrical contacts to sunlight filters in astronauts' helmets. Research now shows how gold at the nanometre scale can be used to exploit light: a sprinkling of gold dust can improve solar cell technology or make more sensitive biodetectors.

"In ancient times, people already knew how to use gold to obtain fantastic and predictable optical effects," says Cesare Umeton, a physicist at the University of Calabria, Italy, who is working on decidedly more modern applications of plasmonics. "You have to use gold and other particles to have particular effects in optics."

Although plasmonic effects occur in a variety of metals, scientists prefer using gold. "For some applications, other materials might have better properties," says physicist Anatoly Zayats at King's College London. But when researchers consider all the properties together, gold usually wins. It works with visible and near-infrared light — wavelengths important for several growing technologies, including photovoltaics, optical communications, biosensors and display technology. It's also malleable in a molecular sense: groups of functional molecules (ligands) can be attached easily. And in applications in which silver or aluminium would be rendered useless in a matter of weeks by oxidization, gold still works.

Plasmons are electromagnetic oscillations that occur at the surface of a metal nanoparticle when it is struck by a photon and is in contact with a dielectric material — an insulator, such as glass, that can store an electrostatic charge. Electrons oscillate in resonance with the frequency of the incoming light, amplifying the light at a particular wavelength to make a colour brighter; which colour depends on the metal in question, the size of the nanoparticle, and the nature of the insulator. Nanoparticles can also act as antennae, collecting light energy and transmitting it to another material.

CAPTURING SUNLIGHT

The ability of metal nanoparticles to act like an antenna is helping Yang Yang, a materials physicist at the University of California, Los Angeles, to improve the efficiency of polymer solar cells — their efficiency at converting sunlight to electricity is counted in single digits, compared with almost 20% efficiency achieved with conventional silicon solar cells. The polymer cells, however, are lighter, simpler and potentially much cheaper.

Yang works on tandem solar cells in which thin films of polymer are stacked on top of one another. Because each layer is made of an organic semiconductor tuned to a different wavelength, the design promises to capture a broader spectrum of sunlight. To make the cells more sensitive, Yang mixes gold nanoparticles about 500–600 nm in diameter into a common conductive polymer called PEDOT, which serves as a connector between the layers. The gold captures light and delivers it to the next layer of semiconductor. "You can think of it as an amplifier," Yang says. Using the gold nanoparticles, Yang increased the efficiency of the tandem solar cell from 5.22% to 6.24% (ref. 1).

With even these modest rates of efficiency, polymer solar cells could become a valuable power source because they can be coated onto windows without the expense or weight considerations of a rooftop silicon installation. "If we can turn half the windows in New York City into solar cells with 5–10% efficiency, I think we can really do something for the solar industry," Yang says. He estimates that in some locations, solar cells applied to the windows of one 30-storey building could provide enough electricity to meet the needs of 25 households[1].

Gold could also improve solar cells in a different way. Zayats makes slits 100 nm wide in thin gold films, with varied spacing between the slits[2]. This produces a plasmonic rainbow effect, where different frequencies of plasmonic waves arise on different parts of the gold grating, interacting with various wavelengths of light. The device acts as a broadband antenna that could, for example, enable a solar cell to capture a wider range of wavelengths. The gratings work equally well regardless of the angle of light, so there is no need to mechanically redirect the panels towards the Sun.

But Zayats thinks his plasmonic rainbow could be more useful in sensors. Many organic molecules can be identified by the infrared light they absorb, but existing detectors don't work well at those wavelengths. A plasmonic grating that focuses light onto a sensor would make them much more sensitive.

Another type of highly effective sensor to detect drugs or explosives could be based on a different way of amplifying light, called surface-enhanced Raman spectroscopy, according to chemists Alexei Kornyshev and Joshua Edel of Imperial College London. Their device is simple: they took gold particles about 43 nm in diameter with molecules of citric acid attached, and mixed these nanoparticles with water, sodium chloride and an organic solvent[3]. The nanoparticles lined up in a thin film at the boundary between the water and the organic solvent. By changing the sodium chloride concentration, they can control the spacing between the nanoparticles: when spaced close together (but not touching), the plasmonic effect creates a 'hot spot' between the nanoparticles that amplifies light by 10–12 orders of magnitude, Edel says.

To test a sample, they mix it in and shine a laser beam on the tube, then analyse the outgoing light with a spectrograph, which splits light into its composite frequencies. A molecule will bind either the citric acid or the gold itself and cause a distinctive spectral shift, amplified by the hot spot. In just a few seconds the sensor can detect a drug, explosive or pollutant present in quantities of just a dozen molecules, according to Edel.

META METAL

Gold can be used to build materials with properties that seem to defy common sense. One such metamaterial attracts light from an area larger than itself. The material, built at Duke University in Durham, North Carolina, consists of a thin film of gold covered with a transparent polymer, with silver nanocubes scattered over the polymer surface at a density of up to 30 million cubes per square millimetre. With the right spacing between the underlying metal and the silver cubes, plasmon resonance alters the electromagnetic properties of the thin film in an area 30 times as large as the cube itself, cancelling out its ability to reflect light[4]. So carefully covering about 3% of a surface could lead to the absorption of all the light striking that surface. "All the light gets trapped under the cube," explains Antoine Moreau, a nanophotonics researcher at Blaise Pascal University in Clermont-Ferrand, France, who worked with the Duke team. Such total absorption might be useful for turning light into heat and then generating electricity in thermophotovoltaics. Engineering the material to control which wavelength it captures could lead to a nano-ink for security printing on currency or seals of authenticity.

Glowing for gold: metal nanoparticles turn the Lycurgus Cup red when light is shone through it.

The first three-dimensional metamaterials that work with infrared or visible light were created in 2008, and they are still expensive and time consuming to produce. But the Duke process relies on self-assembly, selecting the chemical and physical properties of the components so they form the desired structure, just as Edel's sensors do. In fact, much of the appeal of recent work with nanoparticles is that they rely on potentially cheap 'bottom-up' assembly.

SHRINKING ELECTRONICS

Nanoparticles might also serve as the building blocks for nanoelectronics. Umeton, for instance, says that he can build a nanoscale resistance–inductance–capacitance (RLC) circuit, an important component in radio signal filtering and tuning. He does this by mixing gold nanoparticles into liquid crystals in a diffraction grating, which spreads out the wavelengths of light like a prism. Choosing a liquid crystal material with a particular refractive index lets him select which wavelengths to work with, and applying an electric field lets him switch the index between two states[5].

"You can use this in any kind of nanoelectric circuit," Umeton says. "You have the possibility to transfer to the nanoscale the know-how you have for electronics."

The gold-in-liquid-crystal technology could lead to displays built on flexible substrates such as plastic, suggests his colleague at the University of Calabria, physicist Roberto Caputo. "In principle, you would illuminate it with white light and get all the colours you need by using the plasmonic response," he says. With no colour filters, lower energy consumption and the ability to bend, such screens could be wrapped around telephone poles or sewn into clothing.

Gold-based plasmonics could reach inside computers as well. Engineers would like to use light to route data between processors on computer chips, because it can carry much more data quicker than an electrical signal. But as Zayats points out, silicon waveguides to channel the light have diameters of a few hundred nanometres, compared with the tens of nanometres used in electrical connections. Plasmonics offer a solution: they can squeeze light into spaces much smaller than the light's wavelength. Several groups, from Stanford University in California to the University of Twente in Enschede, the Netherlands, are currently developing plasmonic waveguides, and Zayats says they're almost ready for production.

Caputo points to another way gold could speed up computers. Liquid crystals can serve as the basis of microlasers. Caputo says selecting the concentration of gold nanoparticles within these crystals would allow engineers to choose different colours of laser light. A laser array on a chip could provide high-capacity interconnects — yet one more golden opportunity for those tiny flecks of yellow metal to have an outsized impact on technology. ■

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COURTESY OF MINTEK

A material combining gold and titanium dioxide can scrub pollutants from smoke-filled environments.

CATALYSIS

The accelerator

Gold can speed up a multitude of chemical reactions — so why isn't it widely used in industry?

BY MARK PEPLOW

"Ladies and gentlemen, start your engines!" The air fills with the poisonous fumes pouring from the roaring stock cars lined up on the grid at the Daytona 500, the most prestigious race of this year's NASCAR Sprint Cup Series. Inside two of the cars, though, the drivers are breathing easy — their air supply has been scrubbed clean by a gold catalyst called NanAuCat, which uses ambient oxygen to convert carbon monoxide to carbon dioxide.

This is a little-known application of a catalyst that has taken more than two decades to complete the journey from the lab to the racetrack. Back in 1987, chemist Masatake Haruta of the Government Industrial Research Institute of Osaka, Japan, and colleagues showed that tiny particles of gold were remarkably active, helping to unite carbon monoxide and oxygen to make carbon dioxide.

The idea that gold could hasten chemical reactions was deeply counterintuitive for most chemists. After all, gold is famously inert in its bulk form. It has been used for millennia to make jewellery precisely because it does not tarnish by reacting with oxygen or water.

For inorganic chemist Graham Hutchings, however, Haruta's findings chimed with a discovery of his own. A few years earlier, he was hunting for a catalyst to convert acetylene to vinyl chloride — the starting point for a plethora of plastic products that use polyvinyl chloride. The conventional synthesis relied on a mercury (II) chloride catalyst, a source of environmental mercury pollution. Hutchings, now at Cardiff University, UK, checked the standard electrode potentials of a host of alternative metals — a measurement that describes the metal ion's ability to grab an electron — and realized that gold was almost perfectly suited to cosy up to acetylene and accelerate its reactions.

The discoveries by Hutchings and Haruta set the stage for a boom in research on gold's catalytic properties. "The field is still in exponential growth," says Stephen Hashmi, a gold chemist at the University of Heidelberg, Germany. "Even now, every day, people are finding new reactions that use gold catalysts."

Yet despite the slew of research, these two breakthrough reactions remain gold's greatest hits. And neither has been scaled up for use in large-scale chemical production plants, although Haruta's carbon monoxide oxidation has found a few niche applications. The main stumbling block is economic: although gold is not as costly as some other metal catalysts such as platinum, and can be more effective, it has mostly proven too expensive to displace existing technologies.

But the intensive research effort is finally pinning down exactly how gold speeds up chemical reactions, enabling scientists to boost its activity and durability enough to make it suitable for industrial work. Along the way, learning how gold behaves at the nanoscale has led to diverse applications in medicine (see 'The new gold standard', page S14), electronics (see 'Trick of the light', page S8) and motoring.

BREATHE EASY

Away from the thrills of the Daytona 500, gold can be found oxidizing carbon monoxide in a more mundane location: the exhaust pipe of a Fiat.

Platinum is the active ingredient in most catalytic converters, which help to oxidize carbon monoxide, unburned hydrocarbons and other engine emissions in order to reduce pollution. But in 2011, Fiat began installing in some of its diesel vehicles a gold–palladium catalyst — NSGold — developed by start-up Nanostellar of Redwood, California.

Nanostellar's catalyst would have seemed a bargain five years ago when the cost of platinum passed US$70 per gram, more than twice the price of gold. But by the end of 2012, the global economic crisis had squeezed car production, reducing the need for platinum and driving down its price. At the same time, the price of gold rose rapidly as investors sought a safe haven for their cash. Gold now costs almost the same as platinum, in the $50–55 per gram range. "The advantage has pretty much vanished," says materials scientist Kyeongjae Cho of the University of Texas, Dallas, who developed the catalyst and co-founded the company. It is unclear whether Fiat will install any more gold catalytic converters.

Other companies are still betting on the same reaction, albeit in a different context: fire safety respirators. Project AuTEK, a gold technology effort run by South African mining technology company Mintek, in partnership with other mining-industry players, has developed a range of gold catalysts embedded on metal oxides that can scrub pollutants from smoke-filled environments.

Although chemists are still debating exactly how Haruta's reaction works, it seems that the metal oxides bind and activate oxygen from the air, which can then react with carbon monoxide molecules stuck to neighbouring clusters of gold atoms. These can outperform conventional catalysts used in emergency respirators that help people escape burning buildings. Hooded respirators typically bear a cartridge containing Hopcalite, a catalyst that is very good at speeding up carbon monoxide oxidation — but only when dry, explains Nathan Fredericks, a senior researcher on Project AuTEK. That's because water molecules block the active sites of the Hopcalite catalyst, explains Stan Golunski, who studies gold chemistry at Cardiff University. Smoky buildings tend to be humid so the cartridge needs to contain a protective bed to stop the damp air damaging the catalyst, as well as extra sacrificial Hopcalite. These additions result in a bulky, 200–300-millilitre unit.

Gold catalysts, however, are moisture tolerant in up to 95% humidity and, says Fredericks, have a much higher activity than Hopcalite, resulting in better-performing cartridges that are one-tenth the size. What's more, gold atoms can quickly cause water to react with carbon monoxide and eject the products, leaving them free for further reactions.

Novax Material and Technology of Luzhu, Taiwan, for example, already uses this sort of gold catalyst technology in a civilian safety respirator. However, the more recent versions of AuTEK's 2–5-nanometre-wide catalyst particles have higher air flow rates, so firefighters should be able to use them without breathing restrictions, says Fredericks.

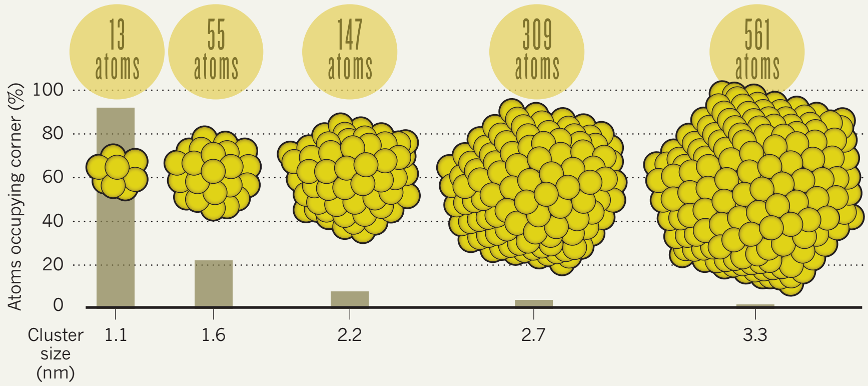
COST CONCERNS

As with all potential applications of gold catalysts, however, "the biggest hurdle is price", admits Fredericks. If that hurdle can be cleared — either by price variations or by improving gold's efficiency — the metal could find new roles in industrial chemical production. Advocates point out that there is already one widely known example of gold being used in this way: the production of the polymer precursor vinyl acetate, an application that actually predates Haruta's and Hutchings' discoveries.

For the past decade or so, the preferred catalyst for producing vinyl acetate has been an alloy of 95% palladium and 5% gold, says Golunski. But this idea dates back to the late 1960s — a patent on a similar catalytic alloy of gold and palladium to make vinyl acetate was issued in 1973.

CORNER CATALYSIS

Gold atoms sitting at the corners of catalyst particles are most able to participate in a chemical reaction. So using smaller clusters of gold atoms can maximize the number of these active atoms.



HARUTA, M. FARADAY DISCUSS 152, 11–32 (2011).

It's a reminder of the sometimes glacial pace of change in the chemicals industry. Many high-volume processes are decades old and built around the use of a specific catalyst, so unless gold can be easily substituted for existing catalysts, it is unlikely that any efficiency savings it offers could offset the enormous costs of building entirely new process infrastructure.

The most promising large-scale applications will be found where gold has little established competition, Golunski says. For example, the stream of hydrogen gas that powers certain types of fuel cell often contains traces of carbon monoxide, which can damage the cells. Chemist Xiao Cheng Zeng of the University of Nebraska-Lincoln has shown that clusters of just 16 to 35 gold atoms can selectively oxidize the carbon monoxide without touching the hydrogen itself, thus extending the fuel cell's lifetime.

SMALL IS BEAUTIFUL

Gold would become a far more cost-effective prospect for industrial catalysis if chemists could improve its activity and durability. Avelino Corma, a gold chemist at the Polytechnic University of Valencia in Spain, last year gave those efforts a boost by showing that clusters of just three to ten gold atoms could efficiently catalyse a previously known reaction of water with alkynes — molecules containing a carbon–carbon triple bond, such as acetylene.

Each cluster could typically catalyse about 100,000 reactions per hour, among the highest ever reported for a gold catalyst. Moreover, each cluster can complete roughly 10 million reactions before losing its potency — a longevity at least ten times greater than that of any other gold catalyst. This performance makes Corma's catalysts a more realistic prospect for use in industry, says Hashmi. "He's in that league now."

Corma's discovery continues the most notable trend in the field: smaller particle size is better. Haruta's work in the 1980s used gold nanoparticles roughly 2–5 nanometres wide, containing hundreds of atoms — most of which were hidden inside the particle and did not participate in any chemical reactions. Of the atoms on the surface, the most active sit at corners or edges, where their electrons are most exposed to incoming reactants (see 'Corner catalysis').

Corma's tiny clusters of atoms measure just a few tenths of a nanometre across, so every gold atom effectively sits at a corner. This strategy dramatically reduces the amount of gold needed — or allows it to be alloyed on the exterior of cheaper metal nanoparticles — potentially slashing the cost.

Corma's next step is to stabilize the catalyst clusters to keep them active for even longer, potentially giving them a greater advantage over existing catalysts. In unpublished work, he says, he has stuck his gold clusters to a solid, inert material that makes the catalyst more durable — and more easily recovered after the reaction — while maintaining the same turnover frequency.

If economics or efficiency cannot propel gold catalysts into widespread use, tighter safety regulations might. In 2011, the US National Fire Protection Association issued revised standards for safety respirators worn while fighting wildfires, increasing the duration of protection against carbon monoxide from 30 minutes to 8 hours. Fredericks says protection for this length of time cannot be achieved using current Hopcalite technology, leaving gold catalysis as the only viable option.

Indeed, it was the importance of safety that put gold in pole position at the NASCAR Sprint Cup. Teams have paid much more attention to air purification since former NASCAR winner Rick Mast retired in 2002, citing ill health from chronic carbon monoxide poisoning. In the end, predicts Fredericks, "people will start to use gold catalysts because they'll have to." ■

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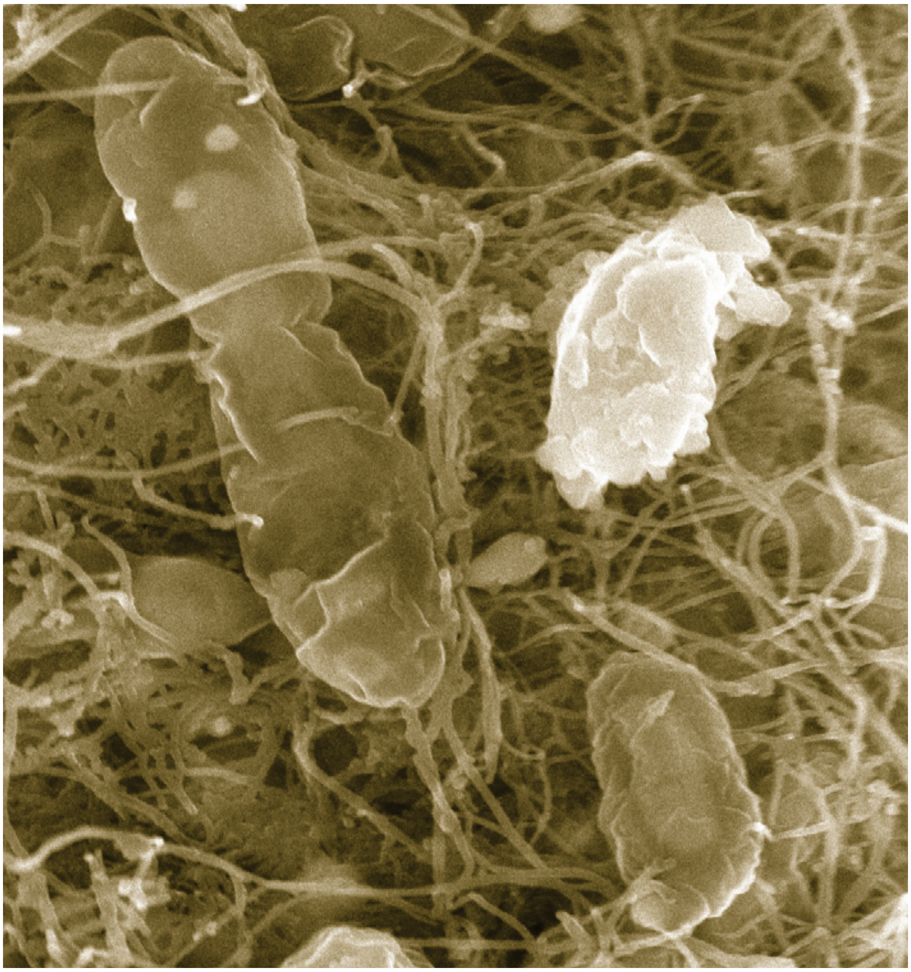

FRANK REITH

Cupriavidus metallidurans **bacteria metabolize toxic gold chloride into gold nanoparticles (white).**

MICROBIOLOGY

There's gold in them there bugs

Microbial 'alchemy' could lead to new ways of detecting and producing the precious metal.

BY PETER GWYNNE

Take a solution of gold chloride, a compound toxic to most forms of life. Add a colony of *Cupriavidus metallidurans*, one of the few bacteria able to survive amid compounds of heavy metals in mines across the world. As the bacteria accumulate the gold salt from the solution, biochemical processes within the organisms reduce it to the pure metal, which the bacteria excrete in the form of tiny gold nuggets — nanoparticles of pure gold. The bacteria produce the gold as protection from the toxic gold complexes that would otherwise destroy their cells.

The process won't inspire a new gold rush, because scaling it up would be both prohibitively expensive and time-consuming, but it does have implications for the creation, detection and processing of this noble metal. And it all relies on extremophile microorganisms that can thrive in environments rich in solutions of salts that are lethal to most forms of life.

Recent findings may lead to bioindicators that can identify microorganisms associated with gold and hence pinpoint the presence of the metal; biosensors that can help prospecting teams quickly determine the concentration of gold in environmental samples; and the biosynthesis of gold nanoparticles, which have potential applications in optoelectronics, imaging technology, catalysis, drug delivery and more. Researchers are also exploring whether bacteria played a role in the creation of gold deposits worldwide. Deeper understanding of the link between bacteria and gold could even lead to bacteria producing customized gold nuggets.

There are economic, environmental and scientific reasons for the current interest in the connection between bacteria and gold. The price of gold has risen by a factor of 4.5 during the past decade (see 'Mine, all mine!', page S2). This leap has made gold mining highly profitable. "But it also means that new deposits have to be found and difficult types of ore have to be processed," says Frank Reith, a geomicrobiologist at the University of Adelaide in Australia.

MICROBIAL ALCHEMISTS

Certain bacteria are "microbial alchemists, transforming gold from something that has no value to a solid, precious metal", according to Kazem Kashefi, a microbiologist and molecular geneticist at Michigan State University in East Lansing. "For millions of years they've been working on gold. They've had enough time to become specialists in gold production." Kashefi and his Michigan State University colleague Adam Brown, an expert in electronic art, have put that specialization to novel use in a work of microbial performance art. Their installation, called *The Great Work of the Metal Lover*, features *C. metallidurans* bacteria producing 24-carat gold from a solution of gold chloride in front of a live audience.

Today, researchers across the world are trying to find extremophiles that can produce pure gold from its compounds. The few types identified to date have been found on land, but researchers in India are searching the seas. "Marine water is known to be the richest source of gold in nature" in the form of gold chloride, says Anirban Roy Choudhury, a specialist in fermentation technology at India's Institute of Microbial Technology in Chandigarh. Choudhury leads a programme that studies the potential of marine microorganisms to create gold nanoparticles. Oceans also have extremely high temperature, pressure and salinity, and harbour heavy metal ions, all of which favour the growth of extremophiles.

Choudhury's team has isolated several types of bacteria from the seas around India and screened them for gold-producing ability. So far, he has found more than 15 species capable of producing gold nanoparticles. One microorganism, *Marinobacter pelagius*, proved particularly effective, rapidly synthesizing gold particles about 10 nanometres in size. The team is now trying to understand how the microbes produce gold nanoparticles. It also aims to develop what Choudhury calls "a suitable production and purification method for gold nanoparticles via biological routes".

GREG KOHUTH/MSU PHOTOGRAPHY SERVICES

Other teams are looking for gold-synthesizing bacteria on land. Geomicrobiologist Gordon Southam, director of the Centre for Environment and Sustainability at the University of Western Ontario in London, Canada, and geochemist Maggy Lengke, who was then a postdoctoral researcher on his team, found three types of bacteria with this ability: *Acidithiobacillus thiooxidans*, sulphate-reducing bacteria and cyanobacteria from a borehole more than three kilometres deep in the Driefontein Consolidated gold mine in South Africa's Witwatersrand Basin[1]. "All three were able to produce solid gold from a gold solution," Lengke says.

Regarding the sulphate-reducing bacteria, "the bacterial precipitation of gold from the gold–thiosulphate solution is linked directly" to the microbes' ability to metabolize sulphur compounds, says Lengke. Such gold-containing solutions have been found in other gold sources, she notes, such as the Wau field in Papua New Guinea and the Ashanti mine in Ghana. The implication is that various types of bacteria may have played a role in the creation of gold deposits throughout the world.

TINY PROSPECTORS

Gold mines in Australia have added to the evidence for the historical role of bacteria in gold production. For his PhD, Reith studied communities of organisms existing in biofilms on the surface of gold grains from two mines. Biofilms from both mines contained *C. metallidurans* that thrived in the presence of toxic gold complexes. Later studies revealed that the biofilms on some of the grains also contained another bacterium, *Delftia acidovorans*, along with gold nanoparticles[2].

Tagging the bacterial DNA enabled the team to monitor the biofilms' chemical activity. "We saw the beautiful active biofilm dissolving the gold," says Reith's colleague Joël Brugger, a geochemist at the South Australian Museum in Adelaide. Some of the dissolved gold was redeposited into nanoparticles that were purer than the original grains. The nanoparticles can be transported through rocks and soils to end up in secondary deposits in cracks and crevices — much as Lengke found.

This dissolve-and-deposit process won't increase the total global supply of gold, but it does suggest two fresh approaches to discovering lodes of gold. "Bioindicator systems can be developed where the detection of certain microorganisms, microbial communities or functions indicates the presence of specific metals," Reith explains.

By using microarrays and DNA sequencing, for example, Reith and geochemist Carla Zammit of the University of Adelaide's Institute for Mineral and Energy Resources, along with fellow researchers, recently showed a correlation between the composition of microorganisms at mining sites and the metals present. The techniques they used included transcriptomic microarrays, to detect up-regulation of gold-inducible genes of bacteria naturally associated with metals; this can indicate what metals are present. The team also used proteomic methods coupled with mass spectrometry to detect gold-binding proteins. Metabolomics enabled them to study the metabolites from biochemical reactions inside bacteria to access the 'chemical fingerprint' of cellular reactions involving metals. "As the costs of these techniques decrease in the future," Reith says, "exploration teams will employ molecular techniques to determine the microbial composition of a site and use this to identify possible sites of mineralization" — places where gold might be found.

In *The Great Work of the Metal Lover*, bacteria produce 24-carat gold for an audience.

Reith's group has shown that genetic information can distinguish between mineralized and unmineralized soils. "There are a few false positives," Brugger notes. "But in general the separation based on genetic information is quite encouraging."

Studies of the link between bacteria and gold are stimulating the development of hand-held biosensors. These will be able to analyse environmental samples for the presence of gold using gold-binding proteins derived from *C. metallidurans* and other bacteria known to coexist with gold — and hence find the precious metal. "Tests show that we reach detection limits of parts per billion in lab solutions with our whole-cell sensor," Reith says. "Exploration teams will be able to obtain information on gold concentrations in an environmental sample on-site, rather than after weeks of laboratory analysis." Reith's team is also developing molecular techniques, such as specific transcriptomic microarrays, that will be able to identify genes from *C. metallidurans* for use in a gold biosensor.

A RICHER HARVEST

Bacteria could also improve the output of established gold mines that have become uneconomic because they contain low-grade ore. Traditional technology leaves behind up to 20% of the available gold (see 'Extreme prospects', page S4). But it might be possible to extract some of that metal by putting bacteria to work. "Using microbial incubation of waste rock piles containing this unrecoverable gold might be a good way to achieve a low-tech, cost-efficient approach to concentrate gold into more recoverable forms," Reith says.

Reith and co-workers from the universities of Adelaide and Halle, Germany, for example, have started studying the biochemical process that catalyses the precipitation of gold from solution in *C. metallidurans*. The research involves the use of a synchrotron and transmission electron microscopy coupled with microarrays to detect the proteins that catalyse the reactions. Reith's team has also developed a method based on high-performance liquid chromatography and inductively coupled mass spectrometry to measure the complexed forms — such as gold chloride or gold thiosulphate — in which gold exists in aqueous solutions[3]. "This is important," Reith says, "because the type of ligand the gold is complexed with determines the mobility, as well as the environmental toxicity, of the complexes, which in turn is important for the biochemical reaction of the bacteria." The goal is to understand how gold exists in groundwater systems.

Researchers from McMaster University in Hamilton, Ontario, and Western Ontario University in London, Canada, recently discovered how *Delftia acidovorans* protects itself from soluble gold compounds. It does this by generating solid gold. The finding, the team notes, is the first demonstration that a secreted metabolite can protect against toxic gold and cause gold biomineralization[4].

Lengke hopes bacteria can be coaxed to produce more of the metal. "Research should focus on better understanding of the mechanisms of gold precipitation, which will enable us to achieve better control over size, shape and uniformity," she says. "That will lead to the development of production-level amounts of gold."

That's a prospect for far in the future, but it would provide a suitable conclusion to a long-running process. "Microbes have been perfecting their biochemical pathways for more than 3.5 billion years," says Zammit. "And we're just starting to realize their potential." ■

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Their size and ability to absorb light are just two of the many qualities of gold nanoparticles that can be controlled — and these changes conveniently alter the colour of their solutions, making them ideal for use in diagnostics.

BIOMEDICINE

The new gold standard

Prized for their versatility, optical properties and safety, gold nanoparticles are helping to image, diagnose and treat disease.

BY KAREN WEINTRAUB

In her lab in Cambridge, Massachusetts, Abigail Lytton-Jean holds up a burgundy-coloured suspension of 15-nanometre gold particles. She pipettes a little into a vial, adds a bit of salt and shakes gently. Suddenly the red liquid turns deep blue. Gold particles carry a slight negative charge, so they repel one another. But the salt interferes with this repulsion and allows shorter-range attractive forces to take over; now, with the particles clumped together, the liquid appears blue. Researchers such as Lytton-Jean, a chemist at the Massachusetts Institute of Technology, can get any colour they like just by 'tuning' the size of the gold particles.

This colour control is one of the key assets of gold in a clinical setting. The size of gold particles, the charge, the hydrophobicity and the shape can all be manipulated to create nanoparticles that can home in on tumours, absorb light, deliver targeted drugs, and slip smoothly into a cell to silence genes.

"You can engineer them to behave nicely," says chemist Vincent Rotello of the University of Massachusetts Amherst, who works with gold nanoparticles. "You can stick a bunch of things on a gold nanoparticle and get it to have very controlled behaviour." It's easy, for example, to cover gold with sulphur atoms, and then you can attach medications, other metals, or almost anything a chemist might want, Rotello says.

Of the roughly 65,000 research papers on nanoparticles listed in PubMed since the first in 1978, more than 15% mention gold, and most of those were in the past 5 years. "It's by far the most studied of these kinds of materials," says Paul Alivisatos, a nanotechnology researcher at the University of California, Berkeley, and director of the Lawrence Berkeley National Laboratory. "Nothing else is even close."

The biomedical use of tiny bits of gold has taken off in the past 3–4 years, largely because the technology is so readily accessible, says Rotello. Fabrication of gold nanoparticles, it turns out, poses few difficulties even to those with limited laboratory experience — indeed, Rotello says, they're so easy to make that high-school students are doing it.

Most of the early biomedical work on nanoparticles (not just involving gold) was in cancer research, which still accounts for nearly 40% of nanotechnology submissions to the US Food and Drug Administration (FDA). Nanoparticles are particularly useful for targeted drug therapy because they move along the bloodstream but get trapped in the porous network of

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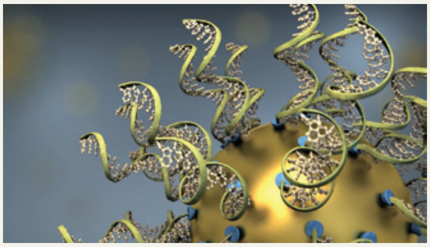
blood vessels that feed a tumour. Now, Rotello says, he and other chemists and bioengineers are branching out, using gold in a variety of applications ranging from detecting infection and gene mutations to experiments that send the nanoparticles across the blood–brain barrier to treat neurological conditions.

Biomedical work with gold nanoparticles can be categorized into four types of research: diagnosis, drug delivery, medical imaging and targeted killing of cells. Research is also beginning on so-called theranostic technologies, which combine diagnostics and treatment in a single procedure. Gold is an ideal theranostic because it can be used in so many different ways, says Dan Peer, a nanotechnologist who runs the nanomedicine lab at Tel Aviv University in Israel. In particular, its reflective nature can be exploited in diagnostics, and its ability to carry other compounds makes it an effective drug delivery platform.

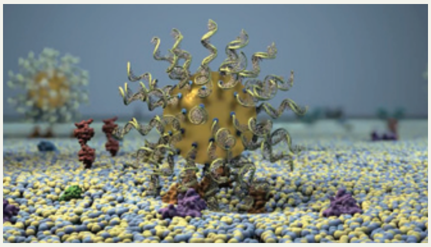
And there's another intangible benefit to working with gold: people are intrigued by the metal, with its deep historical resonances relating to wealth and beauty. They've seen gold in stained glass windows, on the face of Egyptian mummies and in wedding rings. Nanotechnology itself can be traced back to Michael Faraday's early experiments with gold solutions. Gold research, Lytton-Jean says, "has benefited tremendously from its mystique".

STEALTH FIGHTER

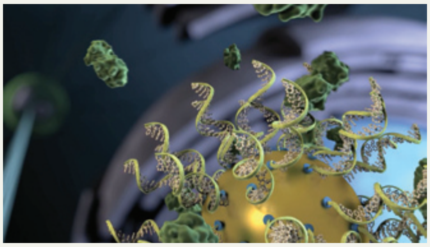
Spherical nucleic acids can pass unharmed into cells to silence genes or deliver drugs.



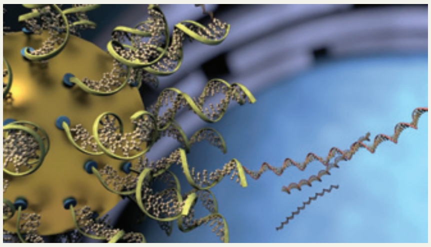
1. Spherical nucleic acids (SNAs) are made by decorating the outside of a gold nanoparticle with single-stranded or double-stranded nucleic acids.



2. Cells readily take in SNAs, which therefore don't need to be packaged inside a virus, for example.



3. The spheres do not trigger an immune response and so are left intact inside the cell.



4. Nucleic acid strands on the sphere pair easily with their complements, allowing genes to be efficiently turned on or silenced.

DIAGNOSTICS

Conducting lab tests used to be the only way to diagnose many diseases and other health problems. A doctor would send a patient's blood sample to the hospital's lab and get results minutes, hours or even days later, by which time the patient's state may have changed. Diagnostics that can produce results quickly and be used in a range of settings, from the operating theatre or doctor's surgery to a rural clinic in Africa, are in high demand.

Taking diagnostics out of the lab requires the technology to be user friendly. Gold is a popular choice for diagnostics that need to be read easily, because it is biologically inert but still links easily to oligonucleotides (short, single strands of RNA or DNA), and it changes colour readily.

A good example of gold-based diagnostics is the FDA-approved Verigene detector. This device, manufactured by Nanosphere, based in Northbrook, Illinois, uses gold nanoparticles coated with oligonucleotides to capture and identify genetic sequences. It can detect a dozen bacteria known to cause infection. Typically, doctors prescribe broad-spectrum antibiotics when they suspect an infection and wait several days for lab results to identify the microorganism responsible. The Verigene detector can identify some infective agents within 2–3 hours, in time to prescribe more specific antibiotics and avoid unnecessary side effects, while limiting the use of broad-spectrum antibiotics that might lead to resistance.

Verigene, based on the research of chemist Chad Mirkin at Northwestern University in Evanston, Illinois, was first approved in 2007 to test whether a patient is sensitive to the blood-thinning drug warfarin. The test is also used to detect the diarrhoea-causing *Clostridium difficile* bacteria and strains of influenza A.

Despite gold's reputation as a precious metal, the gold nanoparticles don't add much to the price of the medical device. Rotello says that even though 90% of his group's lab work involves gold, the metal accounts for only about 0.5% of its budget. According to Nanosphere's chief executive William Moffitt, roughly 35 million of its diagnostic tests can be manufactured from the amount of gold in one man's wedding ring.

TINY TRANSPORTERS

Because it is easy to attach things to gold, gold particles can act as a platform, carrying drugs inside tumours while also controlling their release.

The blood vessels that feed a tumour grow swiftly and are perforated with tiny holes. Nanoparticles that flow through most of the bloodstream get trapped in these pores and hence accumulate in tumours. This neatly sidesteps the problem of how to target treatment, a problem facing most cancer therapies.

The London-based pharmaceutical giant AstraZeneca, for example, recently announced a partnership with nanomedicine company CytImmune of Rockville, Maryland, to jointly develop a method for delivering cancer medication attached to a gold nanoparticle. CytImmune attaches molecules of tumour necrosis factor (TNF) to the surface of the gold particle. The TNF then binds preferentially to the endothelial cells in a tumour's blood vessels and kills them. Indeed, TNF was once a promising cancer treatment itself, but was dropped because it caused an inflammatory response when delivered systemically — a problem neatly overcome by using the gold nanoparticles. CytImmune has completed one phase 1 trial of its gold-plus-TNF drug, called CYT-6091, which showed good safety and tolerance. The company is now collaborating with AstraZeneca to add a chemotherapeutic drug to further improve the killing power, according to CytImmune's chief executive, Lawrence Tamarkin.

Tiny drug scaffolds can also be can used to arrange DNA or RNA into a framework called spherical nucleic acids (SNAs). When Mirkin built SNAs around gold particles and covered their surface with complementary antisense RNA or small interfering RNA, cells took them into the cytoplasm without eliciting an immune response.

The SNAs can easily pass through the skin's outer layer, so a suspension of them in a simple lotion could carry treatments for melanoma and other skin conditions directly to the hard-to-reach target cells[1]. The SNAs can also cross the blood–brain barrier to target glioblastoma cells, Mirkin says. A company developed out of Mirkin's research, AuraSense Therapeutics, based in Skokie, Illinois, has preclinical data on the use of SNAs to treat glioblastoma, solid tumours and various skin diseases, and is working on the clinical development of all three.

Thanks to their ability to penetrate cells, SNAs can deliver oligonucleotides to regulate

gene activity without the need for viruses or other potentially dangerous vectors, Mirkin says. In one recent study[2], Mirkin chemically attached a monoclonal antibody that targets HER2, a growth factor that is implicated in breast cancer, to SNAs. Cells that express HER2 then take up the SNAs. Similar attachments involving a variety of antibodies, peptides, small molecules and other agents might improve the selectivity and potency of SNAs for a variety of gene-based diseases, the study concluded.

HEALING WITH HEAT

Another way to kill cancer cells is to use laser beams, but there are two main problems. One is the difficulty in pinpointing cancerous cells with a laser. The other is that the lethal beams can strike healthy cells. Gold nanoparticles might solve both problems.

Work by researchers including chemist and bioengineer Naomi Halas of Rice University in Houston, Texas, demonstrates that gold nanoparticles of various shapes can absorb near-infrared light[3]. This range of the spectrum easily penetrates tissue without damaging healthy cells. The gold is made to congregate in the tumour, and when the light shines on these nanoparticles, it generates enough heat to kill the adjacent cell or to release drugs from carriers. “That gives you very high precision and very high efficacy” along with minimal side effects, Halas says.

Other work, from teams at the Georgia Institute of Technology in Atlanta and the University of California, San Francisco, has shown that gold nanoparticles optimized for their photothermal capabilities can also help scientists aim their lasers[4]. A company spun off from Halas’s research, Nanospectra Biosciences in Houston, Texas, is conducting a pilot study of head and neck cancers that is due to end in mid-2013 (ref. 5). A trial testing the technology in lung cancer started in late 2012.

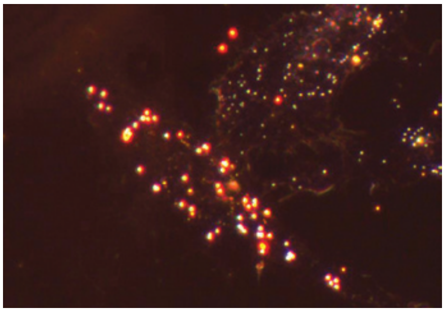
At the heart of Halas’s technology are tiny glass shells coated in gold. These nanoshells are infused into the bloodstream a day before laser treatment. This gives the shells enough time to reach the tumour, but not long enough to be excreted. The nanoshells are coated in the compound polyethylene glycol, which shields the shells from the body’s immune defence[6]. Generally, gold particles of this size are excreted via the liver and kidneys.

The laser beam enters the body through a catheter; a few minutes of illumination ablates the cancer cells. The shells can also be imaged before they are zapped with the laser, helping to diagnose the disease, raising the possibility of using the technology as a theranostic.

These nanoshells might also serve as a delivery vector for gene silencing. Halas has recently shown that single-stranded antisense DNA oligonucleotides or double-stranded short-interfering RNA (siRNA) molecules can be carried on nanoshells and then released when they are exposed to ultraviolet light[7].

A SHARPER EYE

Charles Craik, a pharmaceutical chemist at the University of California, San Francisco, explains his efforts to devise better ways to fight cancer. “When you look at a picture of a field of red poppies, if you look from a very high level, it’s just a smear of red and you don’t know what it is,” he says. “When you go closer, you find it’s a bunch of flowers.” Go even closer, and it’s clear that not all the poppies are red: a few are actually yellow.



Golden glow: gold nanoparticles can enter cells for imaging or to deliver treatments.

CHERYL TAJON, YOUNG-WOOK JUN & CHARLES S. CRAIK

To Craik, the yellow poppies represent the cancer stem cells in a tumour. If he can spot and count these yellow poppy stem cells, he can tell whether a cancer drug has killed them effectively — and therefore whether the cancer is likely to recur after treatment.

But as his metaphor suggests, it isn’t easy to find them. Existing imaging technologies have limitations that make them impractical, he says. Green fluorescent proteins, for instance, emit light only briefly before they bleach out. Quantum dots — nanocrystals that fluoresce when exposed to light — can spot the cells, but the excitation of the crystal’s electrons, which is what makes them visible, also makes them blink on and off, making it impossible to track single cells over time. The quantum dots have another serious drawback as well: they’re toxic.

Gold solves both of these problems, Craik says. When light hits two neighbouring gold nanoparticles, the electrons on each are affected by the other, leading to an effect called plasmonic resonance. As the two particles are moved apart, this resonance “will affect the intensity of the light that’s being reflected, and it will affect the colour”, Craik explains.

One way researchers can exploit plasmonic resonance is by placing gold nanoparticles on either side of a peptide. When the peptide is intact, it appears one colour, Craik says. If the peptide is clipped — by an enzyme associated with cell death, for example — and the gold particles slip farther apart, their colour changes. Thanks to the plasmonic resonance, he says, “you can actually follow single-molecule cleavage.”

This technique, which Craik developed in collaboration with Alivisatos, reveals which cells die during chemotherapy — and, he says, may eventually show whether stem cells are among them[8]. It also makes it easier to track the number of cells killed by various therapies, or the synergistic effects of a combination treatment versus a monotherapy, he says. Gold nanoparticles are “a beautiful tool for looking at synergistic drug therapy”, Craik adds. “They’re so exquisitely sensitive in terms of their ability to look at a single molecule.”

HOW SAFE?

One lingering question about the biomedical use of gold is its safety. Gold is generally presumed to be safe, based on generations, if not centuries, of use. But Peer, of Tel Aviv University, warns against taking this for granted. “If it’s only gold and no surface modification, there is no immune response,” he says. In recent research, he and colleagues, including Rotello, found that modifying the gold surface with hydrophobic residues dictates the immune system’s response[9]. In both *in vitro* and mouse studies, they found that an increase in hydrophobicity is correlated linearly with a rise in immune activation.

And Peer says that although gently activating the immune system could be a good thing in cancer care, it could be a disaster for treating neurodegenerative and inflammatory diseases. He thinks that all new applications of gold nanoparticles should be tested for liver toxicity, kidney toxicity and immune-system activation, and that the FDA should examine the possible hazards of nanoparticles more closely. “We all need to be more careful about how we define toxicity,” he says.

But Halas says that research over the past few years has convinced her of the safety of gold nanoparticles in biomedical applications. “The picture of gold is getting clearer and clearer: it’s boring. It’s non-toxic,” she says.

This safety, along with gold’s versatility and the ease of manipulating it in the lab, suggests that researchers will continue to experiment with gold — and that it will remain the standard against which all other nanomaterials will be judged. ■

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